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Parathyroid function in persistent hyperparathyroidism: Relationship to gland size

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Parathyroid function in persistent hyperparathyroidism: Relationship to gland size. The release of parathyroid hormone in experimental animals is related inversely to the plasma calcium concentration. The relevance, though, of these observations to the dynamics of parathyroid function in normal and hyperparathyroid humans is uncertain. We assessed the in vivo parathyroid hormone response to changes in extracellular calcium in 8 normal subjects and 15 patients with persistent hyperparathyroidism following renal transplantation. In 12 hyperparathyroid patients, the hormone response was related to their total gland size measured at the time of their parathyroidectomy. Plasma-ionized calcium, magnesium, and parathyroid hormone concentrations were measured in the basal state and during a 2-hr infusion of EDTA (50 mg/kg), and a 4-hr calcium infusion (15 mg/kg). The parathyroid function curves of both groups of subjects ($P < 0.001$) fit a log-linear relationship. The slopes of the respective parathyroid function curves were similar, although the hyperparathyroid curve was shifted to the right ($P < 0.0001$). Gland size was not predicted by basal PTH levels; however, it did correlate with changes in parathyroid hormone induced by EDTA ($P < 0.001$) and calcium ($P < 0.001$). We conclude that the in vivo sensitivity of hyperplastic glands to changes in plasma calcium is maintained. The excessive secretion of immunoreactive parathyroid hormone in chief cell hyperplasia primarily reflects total gland mass. Our results indicate that the assessment of the dynamics of parathyroid response, rather than measurements of static plasma parathyroid hormone and calcium concentrations, should be further investigated as a more rational application of radioimmunoassays in the evaluation of the parathyroid axis.

Fonction parathyroïdienne dans l'hyperparathyroidie persistante. Relation avec la taille des glandes. Le relargage de l'hormone parathyroïdienne chez les animaux d'expérience est inversement relié à la concentration plasmatique du calcium. Cependant, la signification de ces observations dans la dynamique du fonctionnement parathyroïdien chez des sujets humains normaux et hyperparathyroïdiens est incertaine. Nous avons étudié in vivo la réponse de l'hormone parathyroïdienne à des modifications du calcium extracellulaire chez 8 normaux sujets et 15 malades ayant une hyperparathyroïdie persistante après transplantation rénale. Chez 12 malades hyperparathyroïdiens, la réponse hormonale a été reliée au poids total de glandes mesuré lors de leur parathyroïdectomie. Les concentrations plasmatiques de calcium ionisé, de magnésium et d'hormone parathyroïdienne ont été mesurées à l'état basal, après une perfusion de 2 heures avec de l'EDTA (50 mg/kg) et après une perfusion de 4 heures par du calcium (15 mg/kg). Les courbes de fonction parathyroïdienne des deux groupes de malades ($P < 0,001$) suivaient une relation log-linéaire. Les pentes des fonctions parathyroïdiennes étaient identiques, bien que la courbe des hyperparathyroïdiens soit déplacée vers la droite ($P < 0,0001$). La taille des glandes n'était pas prévisible par les valeurs de PTH de base; cependant, elle était corrélée avec les modifications de l'hormone parathyroïdienne induites par l'EDTA ($P < 0,001$) et par le calcium ($P < 0,001$). Nous concluons que la sensibilité in vivo des glandes hyperplasiques aux modifications du calcium plasmatique est maintenue. La sécrétion excessive d'hormone parathyroïdienne immunoréactive lors de l'hyperplasie des cellules principales reflète essentiellement la masse glandulaire totale. Nos résultats indiquent que la dynamique de la réponse parathyroïdienne, plus que des mesures statiques des concentrations d'hormone parathyroïdienne et de calcium plasmatique, devrait être étudiée plus avant en tant qu'application plus rationnelle des dosages radioimmunologiques pour évaluer l'axe parathyroïdien.

Experiments using radioimmunoassays for parathyroid hormone [1–9] have provided direct evidence in animals for the importance of the plasma ionized calcium (Ca^{++}) concentration as the predominant determinant of glandular parathyroid hormone biosynthesis and release. Early animal [3, 10] and in vitro [11–15] experiments indicated that the secretion of parathyroid hormone was inversely proportional to the extracellular calcium concentration. Subsequent studies [16–18], particularly ones involving spontaneous and induced hypocalcemia in cows, characterized the relationship by a sigmoid curve.

The relevance of these animal observations to human parathyroid function is uncertain since human studies comparable to those carried out in bovine species [6, 15, 19–23] or in vitro studies using parathyroid tissue from both animals and humans [11, 15, 24–32] are not available. Specifically, the dynamics of the in vivo response of normal subjects to changes in plasma Ca^{++} within the physiologic range and at both extremes of plasma ionized calcium have not been studied systematically, nor have such parathyroid function curves been reported in patients with hyperparathyroidism (HPT). Previous human studies have been limited to comparisons of absolute response of parathyroid hormone concentrations to the infusion of either calcium [33] or EDTA [34–37]. This study was designed to characterize the in vivo response of normal (NL) and hyperplastic human parathyroid glands to both acute hypocalcemia and hypercalcemia and to relate our biochemical data to direct anatomical measurements of gland size.

Methods

Subjects. Eight normal volunteers (three males, five females; mean age, 25 years) comprised the control population. They were screened by history, physical examination, and routine

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laboratory tests for acute and chronic medical disorders and any family history of endocrine diseases. None was taking medication. Their mean (±SD) serum creatinine was 0.9 ± 0.1 mg/dl.

Fifteen patients (seven males, eight females) were selected from the Renal Transplant Clinic at the University of Oregon Health Sciences Center. Selection was based upon biochemical evidence of hyperparathyroidism, that is, persistent hypercalcemia (assessed by measurement of serum total and ionized calcium concentrations), and inappropriately elevated serum parathyroid hormone concentrations. These subjects had good to excellent allograft function (mean, ± SD serum creatinine 1.3 ± 0.3 mg/dl; range, 0.8 to 2.4 mg/dl) at the time of the study. The mean interval post-transplant was 3.5 years (range, 1 to 7 years). All were taking prednisone (range, 7.5 to 15 mg/day) plus either azathioprine or cyclophosphamide in varying dosages. Three transplant recipients were taking propranolol, which was discontinued 14 days before the studies in one. Two patients were maintained on the drug. No patient was receiving vitamin D, oral phosphates, diuretics, cimetidine, or sympathomimetics.

Protocols. The protocols were reviewed and approved by the Committee on Human Experimentation of the University of Oregon Health Sciences Center and the Advisory Committee of the Clinical Research Center. All subjects were admitted to the General Clinical Research Center and informed consent was obtained. Their diet contained 2000 mg sodium (87 mEq), 2000 mg potassium (51 mEq), and 1000 mg calcium per day. A general chemistry screen, complete blood count, urinalysis, EKG, and chest x-ray were obtained on the day of admission. The subjects received, in random order, either a 2-hr infusion of disodium EDTA or a 4-hr infusion of calcium gluconate. All infusions were initiated between 10 and 11 A.M. with the subjects in a supine position; the subjects had fasted since the previous evening. For the infusions, a small gauge, indwelling needle was placed into a superficial vein of the forearm. All blood samples were withdrawn from a vein of the contralateral extremity through a second indwelling needle. Vital signs were monitored every 15 min during the infusions and at frequent intervals postinfusion.

All of the eight normal and 15 HPT subjects received the calcium infusion. Calcium was administered as the gluconate salt at a dose of 13 to 15 mg of calcium per kilogram of body weight. The calcium was placed in 5% dextrose and water (total volume, 1 liter) and infused over 4 hr. Venous blood samples were obtained immediately before (time, 0 min) and at 30, 120, and 240 min during the infusion. Seven of the normal subjects and 12 of the HPT patients were administered disodium EDTA at a dose of 50 mg/kg which was placed in 1 liter (total volume) of 5% dextrose and water. The EDTA was infused over 2 hr. Venous blood samples were collected at time 0 and at 15, 60, and 120 min during the infusion. One to two milliliters of 2% xylocaine were injected around the vein at the site of the infusion needle. Acetaminophen, 600 mg, was given to several subjects to control local discomfort from the EDTA. The infusion rates were held constant by an infusion pump. At all sampling intervals, blood was withdrawn for determination of serum Ca^{++}, magnesium, and parathyroid hormone concentrations.

On two additional days (either day 2, 4, 6, or 8) between 10 and 11 A.M., venous blood samples were withdrawn from the forearm vein. These samples served as additional baseline data for each subject for each of the parameters measured during the infusions. A minimum of 48 hr separated either the infusions and/or the baseline samples obtained in each subject. All of the subjects tolerated the infusions without complications.

Parathyroid gland measurements. Twelve HPT transplant recipients underwent surgical exploration of the neck. Six of these individuals were among the HPT subjects originally studied in the Clinical Research Center protocol. The other six surgical candidates (three males, three females) had also been followed in the Transplant Clinic. Their mean ± SD serum creatinine was 1.2 ± 0.2 mg/dl (range, 0.8 to 1.7 mg/dl) and their mean time after transplantation was identical to that of the first group (3.5 years). All six received an EDTA infusion, and three of them also received a calcium infusion following identical protocols, as outlined above with the exception that immunoreactive PTH was measured in only one assay (anti-PTH-1). All 12 of the HPT subjects were referred for total parathyroidectomy because of clinical complications (neuropsychiatric disorders, metabolic bone disease, vascular calcifications) of hyperparathyroidism or persistent, severe hypercalcemia. (Ca^{++} > 2.8 mEq/liter or total calcium > 12.0 mg/dl). The mean time for all the surgical patients between the infusions and surgery was 7 weeks.

At the time of surgery, a careful dissection of the neck and upper mediastinum was performed; all suspected parathyroid tissue was identified and excised. Immediately after excision each specimen was trimmed of fat and measured in three dimensions before either being placed in preservative or implanted in the nondominant forearm. Confirmation of each specimen's cell type was made by both frozen section examination and by light microscopic examination of the permanent pathologic sections. One trained observer made and recorded all the measurements in these 12 patients. Parathyroid gland volume was calculated using the three dimensional measurements.

Analytical methods. Venous blood samples were collected in 10 ml glass vacutainers, chilled immediately and, within 30 min, centrifuged at 4° C. The serum was separated, placed in plastic vials and stored at −20° C. Magnesium concentrations were determined by atomic absorption spectrophotometry. Ca^{++} was measured directly (NL values = 2.14 ± 0.08 mEq/liter, mean ± SD) (Applied Medical Technologies, Palo Alto, California) [38, 39]. All analyses for magnesium and Ca^{++} were performed in duplicate, and a mean value was reported.

In the initial studies of the HPT subject, immunoreactive parathyroid hormone was determined in two different assays. Both assays used antibovine PTH antisera raised in guinea pigs by repeated subcutaneous immunization with highly purified bovine PTH as well as trichloroacetic acid extract from bovine parathyroid gland (Inolex, Biomedical Division, Wilson Pharmaceutical and Chemical Corp., Glenwood, Illinois). Complete immunochemical characterization of the two antisera was established from tracer displacement studies by highly purified preparations of bovine and human PTH 1-84, natural bovine 53-84, synthetic human and bovine 1-34, synthetic human 53-84, 44-68, bovine 28-48 (all fragments kindly supplied by Dr. John T. Potts, Jr., Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts), as well as selective clinically

diagnosed hyperparathyroid sera and parathyroid gland effluent.

Antiserum GP101 proved to contain two distinct populations of antibodies in about equal concentration and of approximately equal affinity for the amino- and carboxyl-terminal sequence of human and bovine PTH (N/C, biterminal antiserum). Antiserum Anti-PTH-1 (C-antiserum) almost exclusively interacts with the carboxyl 53-84 region of bovine and human PTH; more than 75 and 90% of the tracer is displaced by natural bovine 53-84 and synthetic human 53-84, respectively. Less than 5% of the tracer is displaced competitively by 10,000-fold molar excess of synthetic bovine or human PTH 1-34. Cross reaction of human PTH 1-84 with bovine PTH 1-84 is about 50% for anti-PTH-1 and 30% for the biterminal antiserum GP101. When, however, immunoreactive PTH present in primary and secondary hyperparathyroid serum is analyzed, a three- to fourfold higher cross reaction is exerted by anti-PTH-1 than by the biterminal antiserum.

Highly purified bovine PTH 1-84 was labelled with Iodine-125 by a modified method of Greenwood, Hunter, and Glover [40] which uses only a 17-fold molar excess of chloramine-T over the hormone. The same monoiodinated tracer with an immunoreactivity of at least 85% was used in both assays.

Pooled human hyperparathyroid serum was used as standard in the biterminal (N/C) assay, while both the human hyperparathyroid pooled serum and highly purified bovine PTH 1-84 were used as standards in the carboxyl-terminal specific (C) assay. Comparison of immunochemical potencies of these two standards in the C-assay has shown that 1 ng of bovine PTH 1-84 is equal to approximately 50 μl of the human hyperparathyroid serum pool.

Immunoreactive PTH of previously unthawed sera was determined at 4° C in a 3-day nonequilibrium assay based on the biterminal antiserum and a 3-day equilibrium assay using the C-terminal specific antiserum. Separation of bound from free tracer was accomplished with a second antibody (goat anti-guinea pig gamma globulin, Antibodies Incorporated, Davis, California). All sera from each subject's infusion were analyzed in duplicates in the same assay.

The interassay coefficients of variation for the biterminal assay were 14.5, 12.0, and 10.7% for pools with a mean PTH concentration of 50, 103, and 742 μlEq/ml, respectively, and 6.2 or 13.9% for serum pools with a mean PTH concentration of 1.5 and 27.6 ng equivalent bovine PTH 1-84/ml, respectively, for the N/C-assay. Twenty-five microliter equivalents per milliliter is the lower limit of detection for this assay.

The interassay coefficient of variation for the biterminal assay was 10.6% and 9.2% for a serum pool of 103 and 742 μlEq/ml, respectively, and 8.1 or 16.3% for a serum pool of 2.4 or 18.3 ng equivalent bPTH 1-84/ml, respectively, for the C-assay. Twenty microliter equivalents per milliliter is the lower limit of detection for this assay.

ANOVA, t-statistics and linear regression analyses were used in the analysis of the data. In addition, the analysis of the PTH concentrations by the interval calcium values utilized the method described by Blum et al [6, 7].

Results

EDTA infusions. Figures 1**A** and **B** portray the effect on the serum magnesium, ionized calcium and parathyroid hormone concentrations (as measured by the two assays) in the NL and HPT subjects, respectively, during the EDTA infusion. Magnesium was unchanged in both groups. Ca^{++} levels declined beginning at 15 min ($P < 0.001$) in both NL and HPT and continued to decrease throughout the 120 min ($P < 0.001$). The mean decrease in Ca^{++} [0.45 mEq/liter (NL) versus 0.96 mEq/liter (HPT)] was significantly different ($P < 0.001$) for the two groups. PTH_{GP101} was increased significantly in both groups ($P < 0.001$). There was no further increase in the NL's PTH concentration after 60 min. The mean maximal change in PTH_{GP101} of 54 μlEq/ml (NL) versus 529 μlEq (HPT) was significantly different ($P < 0.001$). While PTH, as measured by antiserum, anti-PTH-1 progressively increased ($P < 0.001$) in both NL and HPT, the rise for both the NL and HPT subjects was less than that detected by the biterminal assay (GP101). The NL's maximal change in $PTH_{anti\text{-}PTH\text{-}1}$ (0.27 ng/ml) was significantly less ($P < 0.001$) than that detected in the HPT (4.24 ng/ml) subjects.

Calcium infusions. Figures 2**A** (NL) and **B** (HPT) depict the response of the same four parameters (Mg, Ca^{++}, PTH_{GP101}, $PTH_{anti\text{-}PTH\text{-}1}$) to the calcium infusions. Serum magnesium was unaffected in the HPT subjects while the NL subjects experienced a transient decline at 120 min. Ca^{++} increased progressively in both groups ($P < 0.001$). The average maximal increase in Ca^{++} for the NL's (0.76 mEq/liter) was not statistically different from that achieved in the HPT patients (1.14 mEq/liter), as there was a wide variation in the transplant patients' response. PTH measured in assay GP101 progressively ($P < 0.001$) declined in both NL and HPTH subjects. Both groups experienced an immediate, significant ($P < 0.01$) decline in PTH_{GP101} during the first 30 min followed by a plateau and then a later, further fall in PTH that was also significant ($P < 0.01$). The mean NL subjects' decline in PTH_{GP101} (19 μlEq/ml) was less ($P < 0.001$) than the HPT subjects' (72 μlEq/ml). $PTH_{anti\text{-}PTH\text{-}1}$ was unchanged in the NL while the HPT patients demonstrated a progressive decrease ($P < 0.001$). As with the EDTA infusions, the antiserum GP101 again proved more sensitive than anti-PTH-1 to the changes in the immunoreactive PTH that occurred.

Parathyroid function curves. Figure 3**A** shows the concentration of PTH as measured in both assays grouped according to intervals of Ca^{++} and then plotted against those mean values of serum Ca^{++}. Beside the infusion data, the additional baseline observations are included in this graph. This transformation of the data is identical to that used by Blum, Mayer, and Potts [6], Blum et al [7], Mayer and Hurst [22, 23], and Keaton et al [21] in their reports of similar studies in bovine species. The acute response of the normal parathyroid gland to changes in serum Ca^{++} is nonlinear. Because of the greater sensitivity of the antiserum with both NH_2- and COOH-terminal antigenic specificity, the nonlinear relationship between serum PTH and Ca^{++} is more apparent with the GP101 antiserum.

The data for the HPT subjects analyzed in the same fashion is shown in Figure 3**B**. As noted above, the HPT patients experienced a greater degree of induced hypercalcemia and hypocalcemia. Consequently, 14 intervals of calcium are plotted. A nonlinear, relationship between serum PTH and Ca^{++} is evident, and a plateau value for PTH is suggested. As with the NL subjects' parathyroid function curves, the assay with NH_2- and COOH-terminal specificity better defined the nonlinear nature

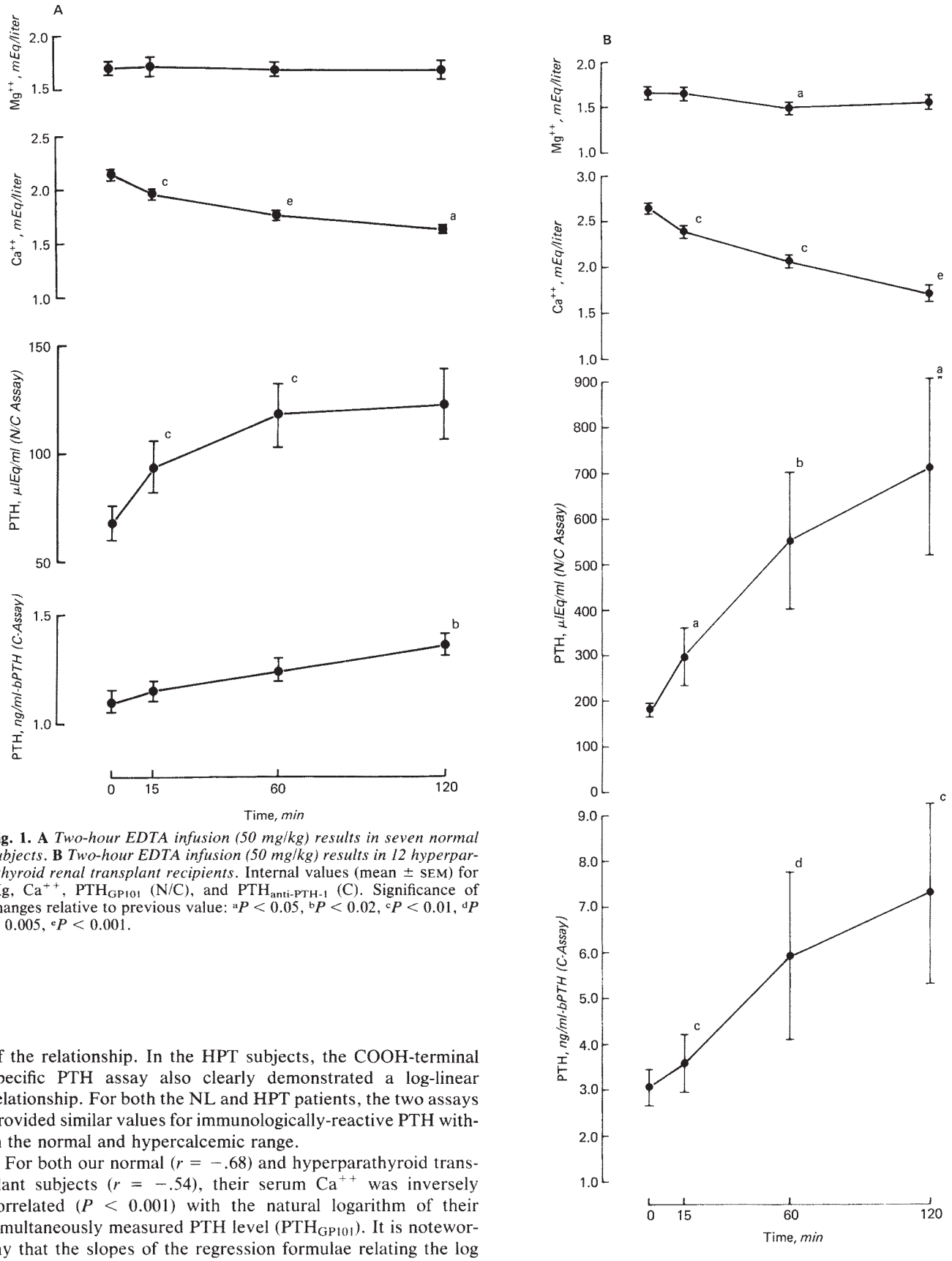

Fig. 1. A *Two-hour EDTA infusion (50 mg/kg) results in seven normal subjects.* **B** *Two-hour EDTA infusion (50 mg/kg) results in 12 hyperparathyroid renal transplant recipients.* Internal values (mean ± SEM) for Mg, Ca^{++}, PTH_{GP101} (N/C), and $PTH_{anti\text{-}PTH\text{-}1}$ (C). Significance of changes relative to previous value: $^aP < 0.05$, $^bP < 0.02$, $^cP < 0.01$, $^dP < 0.005$, $^eP < 0.001$.

of the relationship. In the HPT subjects, the COOH-terminal specific PTH assay also clearly demonstrated a log-linear relationship. For both the NL and HPT patients, the two assays provided similar values for immunologically-reactive PTH within the normal and hypercalcemic range.

For both our normal ($r = -.68$) and hyperparathyroid transplant subjects ($r = -.54$), their serum Ca^{++} was inversely correlated ($P < 0.001$) with the natural logarithm of their simultaneously measured PTH level (PTH_{GP101}). It is noteworthy that the slopes of the regression formulae relating the log PTH and Ca^{++} were similar (NL = −0.59 versus HPT = −0.6);

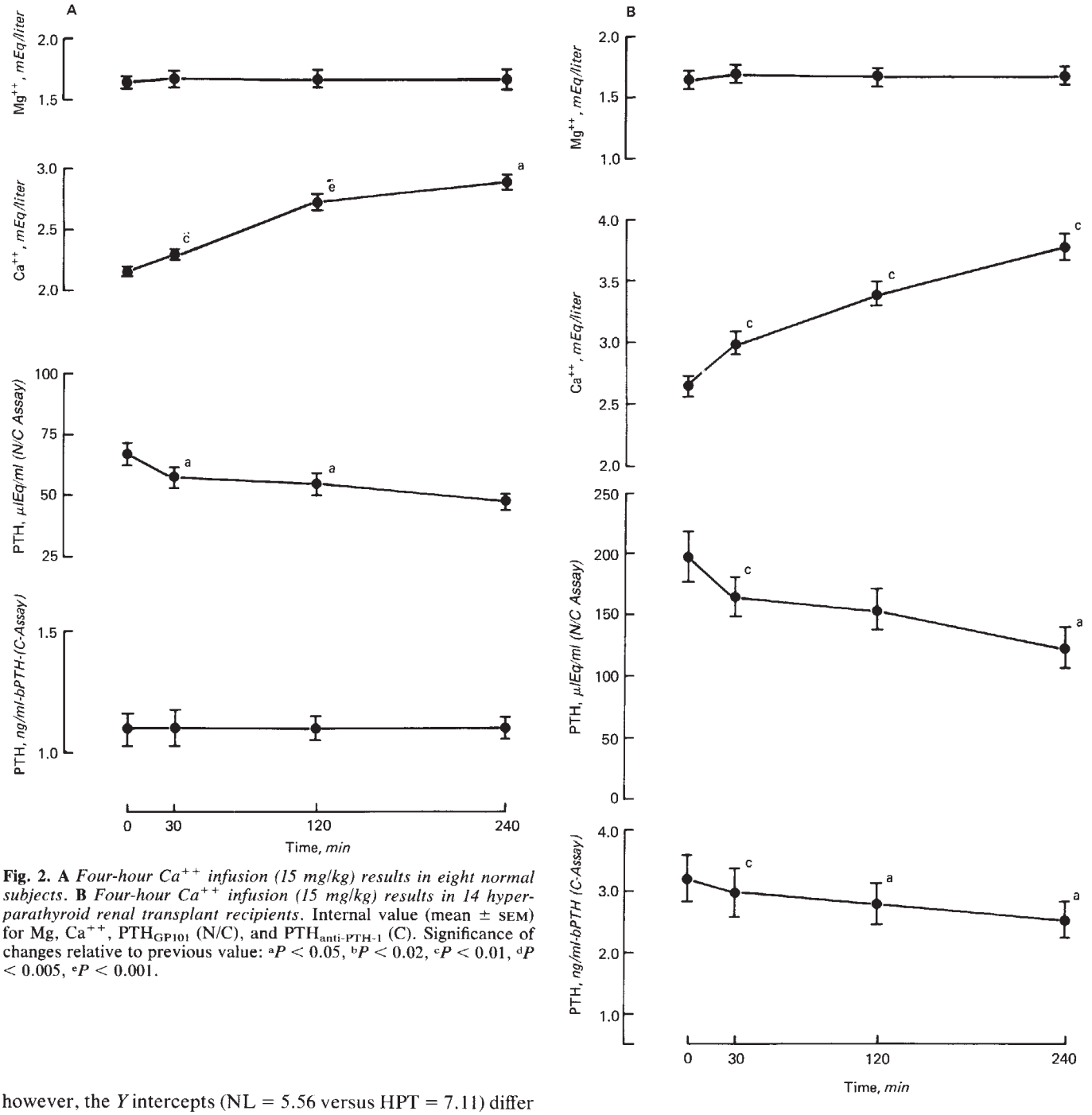

Fig. 2. **A** *Four-hour Ca^{++} infusion (15 mg/kg) results in eight normal subjects.* **B** *Four-hour Ca^{++} infusion (15 mg/kg) results in 14 hyperparathyroid renal transplant recipients.* Internal value (mean ± SEM) for Mg, Ca^{++}, PTH_{GP10} (N/C), and $PTH_{anti\text{-}PTH\text{-}1}$ (C). Significance of changes relative to previous value: $^{a}P < 0.05$, $^{b}P < 0.02$, $^{c}P < 0.01$, $^{d}P < 0.005$, $^{e}P < 0.001$.

however, the *Y* intercepts (NL = 5.56 versus HPT = 7.11) differ ($P < 0.001$). This is indicative of the HPT curve being shifted to the right, that is, at any level of serum Ca^{++} the HPT patients' PTH concentrations are significantly greater.

Parathyroid hormone response and gland size. Twelve HPT transplant recipients underwent total parathyroidectomy with forearm reimplantation. The correlation ($r = 0.5055$) of basal PTH values (c assay) with gland volume was not significant. The absolute change (Δ) in the immunoreactive PTH ($\Delta PTH_{2\ hr\ EDTA}$) that occurred between time 0 min and the end (120 min) of the EDTA infusion is graphed as a function of gland volume in Figure 4. The $\Delta PTH_{2\ hr\ EDTA}$ was correlated significantly ($r = 0.98$, $P < 0.0001$) with the gland volume. The concentration of PTH at the end of the EDTA infusion also correlated with the gland volume ($r = 0.9663$, $P < 0.0001$).

Figure 5 depicts the relationship between the absolute Δ in PTH levels induced by the Ca^{++} infusion and the gland volume. The degree of PTH suppression achieved was correlated closely with gland volume ($r = 0.99$, $P < 0.0001$). In contrast to the stimulation of the gland, suppression of PTH occurred as a nonlinear function of gland volume. The maximally suppressed (4 hr) value of PTH also correlated ($r = 0.93$, $P < 0.0001$) well with the gland volume.

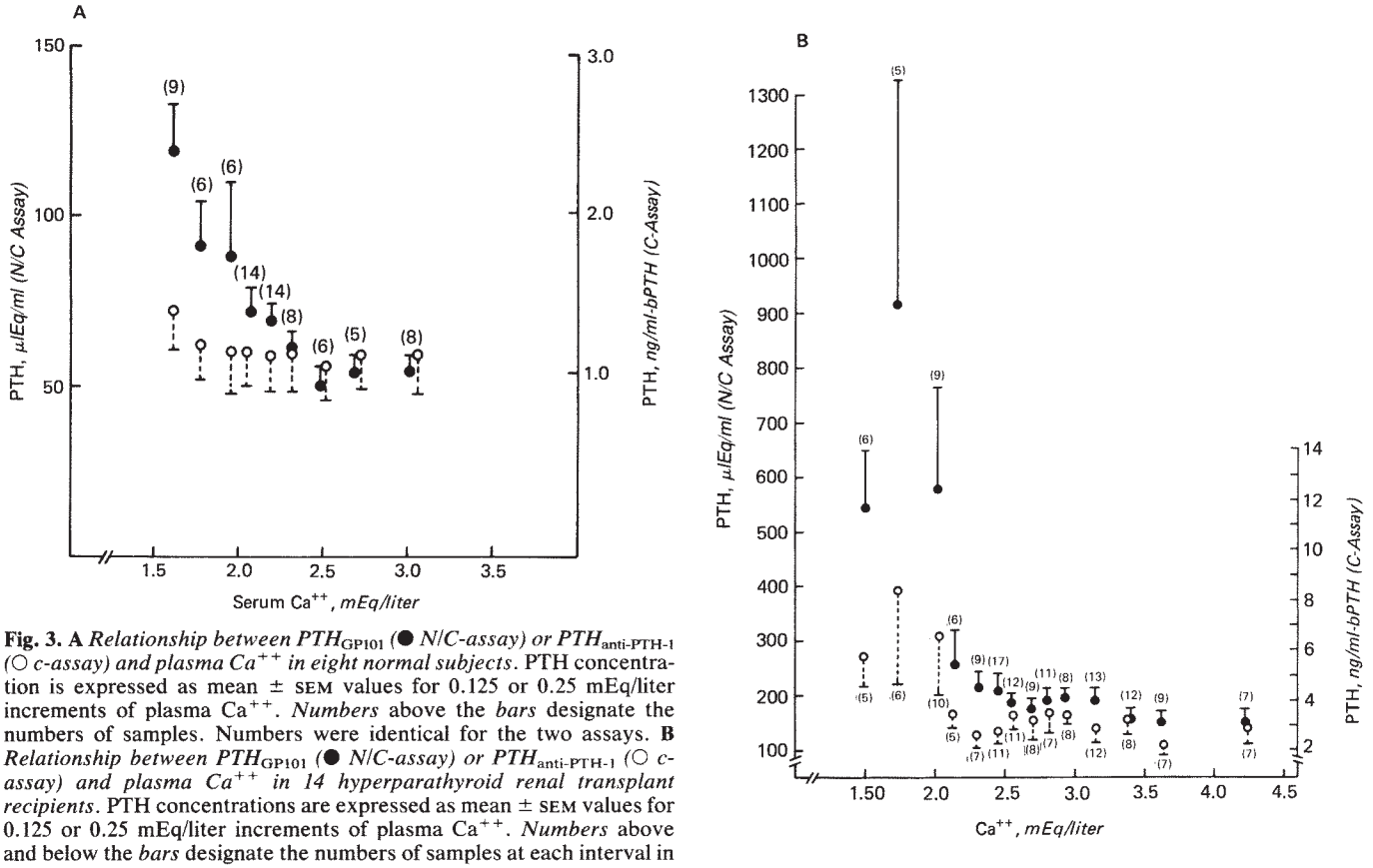

Fig. 3. A *Relationship between* PTH_{GP101} (● *N/C-assay) or* $PTH_{anti\text{-}PTH\text{-}1}$ (○ *c-assay) and plasma* Ca^{++} *in eight normal subjects.* PTH concentration is expressed as mean ± SEM values for 0.125 or 0.25 mEq/liter increments of plasma Ca^{++}. *Numbers* above the *bars* designate the numbers of samples. Numbers were identical for the two assays. **B** *Relationship between* PTH_{GP101} (● *N/C-assay) or* $PTH_{anti\text{-}PTH\text{-}1}$ (○ *c-assay) and plasma* Ca^{++} *in 14 hyperparathyroid renal transplant recipients.* PTH concentrations are expressed as mean ± SEM values for 0.125 or 0.25 mEq/liter increments of plasma Ca^{++}. *Numbers* above and below the *bars* designate the numbers of samples at each interval in each assay.

Discussion

Previous animal experiments [3, 10] and in vitro studies of parathyroid gland explants from both animals and humans [11–15] demonstrated that regulation of parathyroid hormone release is inversely proportional to the plasma Ca^{++} concentration. Blum, Mayer, and Potts [6] characterized the acute in vivo bovine parathyroid hormone response to alterations in plasma Ca^{++} levels as a sigmoid curve. Derivative experiments by these investigators in the same bovine model confirmed that the acute changes in immunoreactive PTH detectable in venous samples were a valid reflection of actual secretory rates of the gland [22]. Data presented in several in vitro studies [15, 24, 32] using human parathyroid tissue have also suggested a nonlinear response of glandular tissue to changes in extracellular Ca^{++}. Recently, the in vitro response of human parathyroid tissue to acute hypercalcemia has been correlated with the in vivo response as measured by PTH levels in peripheral venous samples [16] and nephrogenous cyclic adenosine monophosphate excretion [9, 25].

The inverse, curvilinear relationships described in this study are remarkably similar to the previously defined sigmoid parathyroid gland function curves reported in experimental animal models [6, 21–23]. Numerous human and in vitro [16, 17, 24–26, 28] experiments have demonstrated that release of hormone by hyperplastic glands will decrease with acute hypercalcemia. The responsiveness to acute hypocalcemia, though, in these states has not been as well defined. In the current study, the sensitivity of HPT glands to both acute hypocalcemia and hypercalcemia is well preserved and demonstrates response characteristics that parallel those of NL subjects. If the regulation of hyperplastic glands by plasma Ca^{++} was markedly impaired, the slope of the two response curves should have been significantly different. This was not the case. The parathyroid function curve of the transplant recipients are simply shifted to the right. Keaton et al [21] noted a similar effect in the neonatal calf, an experimental model of parathyroid hyperplasia. These findings indicate that the sensitivity of the hyperplastic gland to acute changes in plasma calcium in vivo is well maintained.

The high plasma concentrations of immunoreactive PTH, detectable despite extreme hypercalcemia in the HPT patients, probably reflect obligatory secretion of carboxyl-terminal hormone fragments by the increased mass of parathyroid tissue, as suggested by other investigators [28–30, 41, 42]. Proportionally, secretion of these fragments increases as extracellular calcium rises. The secretion of peptide fragments is believed to be a normal response of the parathyroid cells rather than a primary defect in the glandular tissue's feedback regulation by calcium, as suggested by earlier investigations. Although impaired clearance by the transplanted kidney of the carboxy-terminal fragments could contribute to the excessive levels of immunoreactive PTH, the good to excellent graft function of our subjects makes this less likely. Impaired renal clearance would also be

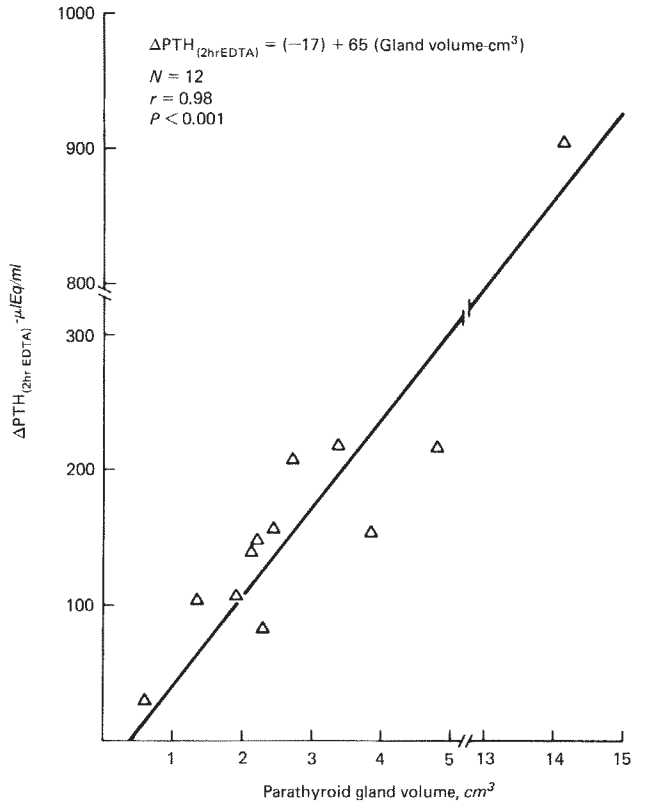

Fig. 4. *Relationship of total parathyroid gland size (cm^3) of ten HPT patients measured at surgery and the maximal (2-hr) change (△) in PTH induced by the EDTA infusion.* The C-terminal (anti-PTH-1) assay utilizing the pooled hyperparathyroid serum is portrayed.

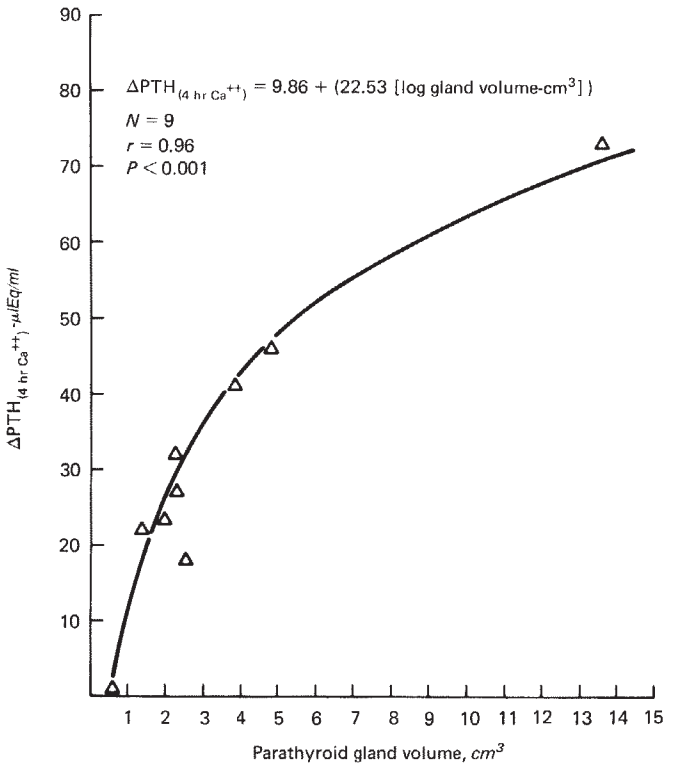

Fig. 5. *Relationship of total parathyroid gland size (cm^3) of nine HPT subjects measured at surgery and the maximal (4-hr) change (△) in PTH induced by the Ca^{++} infusion.* The C-terminal (anti-PTH-1) assay utilizing the pooled hyperparathyroid serum is portrayed.

expected to change the slope of the function curve in patients with parathyroid hyperplasia, which was not the situation.

Hyperparathyroidism after renal transplantation has been considered the prototype of diffuse hyperplasia of the parathyroid glands. Persistent HPT has been thought by some authors to represent a primary failure of feedback inhibition by Ca^{++}, that is, gland autonomy. The fact that gland responsiveness [16, 17, 24–26, 28, 33, 35] and sensitivity to changes in plasma calcium is retained by hyperplastic parathyroid glands implies that an increased total number of parathyroid cells, and not an obligate change in gland sensitivity, is the major defect in post-transplant parathyroid hyperplasia. The recent report of Brown et al [43] concluded that a similar situation existed in parathyroid glands from uremic subjects. Those studies were performed in vitro in a dispersed cell system. The close correlation of total gland size with the in vivo secretory response ($\Delta PTH_{2\ hr\ EDTA}$) of the hyperplastic gland is also consistent with that hypothesis.

In addition, our findings demonstrate the possible utility of measuring the maximal acute secretory capacity of the parathyroid glands as an index of functioning gland mass. Additional clinical investigation would appear to be warranted based upon these initial observations. Such an index would provide a parameter that could be determined periodically to evaluate the progress or regression of parathyroid hyperplasia. The advantage of assessing the dynamics of parathyroid function rather than measurement of only static basal parameters is further evident from the close correlation of the suppression of parathyroid function ($\Delta PTH_{4\ hr}\ Ca^{++}$) and the total gland volume.

The hypothesis that "stimulated" parathyroid hormone levels may provide a better assessment of the human parathyroid gland-calcium axis is consistent with the parathyroid gland ultrastructural studies of Altenahr et al [9]. They noted that basal immunoreactivity of PTH correlated less well (r + 0.68) with gland weight than with a morphometric index (r + 0.95) which included gland weight and estimations of percent volume of parathyroid cells filled with mitochondria, secretory granules, golgi apparati, and glycogen. Ultrastructural analysis was done by electromicroscopy of surgical specimens from patients with "chief-cell adenomas." This study was limited by the necessity to estimate total gland weight, as total parathyroidectomies were not done. Even with that limitation, their findings also demonstrate the ultimate importance of determining the secretory or functional capacity of the parathyroid glands to predict accurately the presence and magnitude of parathyroid gland hyperfunction.

In conclusion, we have demonstrated that the in vivo response curve of normal human parathyroid glands to acute changes in plasma calcium is nonlinear. Renal transplant recipients with persistent parathyroid hyperplasia exhibit a similar parathyroid function curve, although it is shifted to the right, principally due to increased gland mass. Sensitivity of these

hyperplastic parathyroid glands to changes in plasma Ca^{++} concentration appears to be preserved. Because of the heterogeneous nature of circulating immunoreactive PTH, it is often difficult to predict accurately the presence of gland dysfunction by radioimmunoassay of basal PTH. Our results suggest that assessment of parathyroid gland functional or secretory capacity by perturbatory maneuvers may provide a more reliable discriminatory index of parathyroid gland mass in hyperparathyroidism. Future clinical investigations are required to determine whether or not this represents a more rational application of the radioimmunoassay of PTH, in the evaluation of the parathyroid gland-Ca^{++} axis.

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